PATENT

Attorney Docket No.: MEDIV2010-4

In re Application of: Epstein et al.

Application No.: 10/618,183

Filed: July 10, 2003

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In the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Upon entry of the present amendment, the claims will stand as follows:

Please cancel claims 1, 2, 4-8, 13, 14-16, 19, 20-23, 33, 35-38,

Please amend claims 17, 19, 24, 25, 29-32, 34, 39, 40, 43 and 46 as follows:

17. (Currently Amended) A method for enhancing collateral blood vessel formation in heart or limb muscle tissue of a patient in need thereof, said method comprising:

obtaining autologous bone marrow from the patient;

growing the autologous bone marrow in a suitable medium under suitable culture conditions for a period of time sufficient to promote production by the bone marrow of early attaching cells;

transfecting at least a portion of the early attaching cells with an adenovirus vector comprising a polynucleotide that encodes one or more agents selected from hypoxia inducing factor 1 (HIF-1), endothelial PAS domain protein 1 (EPAS1), Monocyte Chemoattractant Protein 1 (MCP-1), granulocyte monocyte colony stimulatory factor (GM-CSF), a fibroblast growth factor (FGF), a NOS, and PR39 so as to cause expression of the one or more agents to produce conditioned medium; and

directly administering to injecting into a site of impaired blood flow in heart or limb muscle tissue of the patient an effective amount of the transfected early attaching cells and/or the conditioned medium to enhance collateral blood vessel formation at the site in the patient obtained from autologous bone marrow, which cells have been transfected with an adenoviral vector comprising a polynucleotide encoding one or more angiogenic factors selected from hypoxia inducing factor-1 (HIF-1), endothelial PAS domain protein 1 (EPAS1), Monocyte Chemoattractant Protein 1 (MCP-1), granulocyte-monocyte colony stimulatory factor (GM-CSF), PR39, a fibroblast growth factor (FGF), and a nitric oxide synthase (NOS).

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Claim 18 (Cancelled)

19. (Currently Amended) The method of claim [[18]] 17, wherein the early attaching cells are marrow-derived stromal cells and the conditioned medium is transfected cells are directly administered to injected into a site of ischemia in the patient muscle tissue.

Claims 20-23 (Cancelled)

- 24. (Currently Amended) The method of claim [[23]47, wherein the period of culturing is from about 3 hours to about 3 days.
- 25. (Currently Amended) The method of claim [[18]] 17, further comprising filtering bone marrow prior to culturing of the bone marrow to obtain the early attaching cells.

Claims 26 - 28 (Cancelled)

- 29. (Currently Amended) The method of claim [[18]] 17, wherein the agent is selected from a fibroblast growth factor (FGF), a NOS, and PR39.
- 30. (Currently Amended) The method of claim [[29]] 17, wherein the agent is selected from FGF-1, FGF-2, FGF-4, and FGF-5.
- 31. (Currently Amended) The method of claim [[29]] <u>17</u>, wherein the agent is selected from inducible NOS and endothelial NOS.
- 32. (Currently Amended) The method of claim [[29]] 17, wherein the agent is PR39.
- 33. (Cancelled)

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34. (Currently Amended) The method of claim [[18]] <u>17</u>, wherein the method enhances collateral blood vessel formation in the heart or leg muscle <u>tissue</u>.

Claims 35 - 38 (Cancelled)

- 39. (Currently Amended) A therapeutic composition comprising early attaching cells derived obtained from bone marrow, which cells have been transfected with an adenoviral vector comprising a polynucleotide that encodes one or more agents selected from hypoxia inducing factor-1 (HIF-1), endothelial PAS domain protein 1 (EPAS1), Monocyte Chemoattractant Protein 1 (MCP-1), granulocyte-monocyte colony stimulatory factor (GM-CSF), PR39, a fibroblast growth factor (FGF), and a nitric oxide synthase (NOS).
- 40. (Currently Amended) The therapeutic composition of claim 39, further comprising conditioned medium in which the cells have been grown in culture for a time sufficient to allow expression of containing one or more of the agents expressed from the polynucleotide.
- 41. (Original) The composition of claim 39, wherein the polynucleotide further comprises a transcription regulatory region operatively associated with the polynucleotide.
- 42. (Original) The composition of claim 39, wherein the transfected cells have been stimulated by exposure to hypoxia.
- 43. (Currently Amended) The composition of claim 39, further comprising heparin or another an anticoagulant.
- 44. (Cancelled)

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45. (Original) The composition of claim 39, wherein the early attaching cells are marrow-

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derived stromal cells.

(Original) The composition of claim 39, wherein the composition is intended to be injected 46.

into a patient having ischemic tissue and the early attaching cells are derived from bone marrow

obtained from the patient.

Please add the following new claims:

47. (New) The method of claim 17, further comprising, prior to the injecting, culturing the

early attaching cells in a culture medium to produce conditioned medium containing one or more

of the agents expressed from the polynucleotides, and wherein the method further comprises

injecting the one or more agents in the conditioned medium along with the transfected early

attaching cells..

(New) The method of claim 17, wherein the injecting is at multiple sites in the muscle 48.

tissue.

(New) The method of claim 48, wherein the effective amount is about 0.2 to about 0.5 ml 49.

of the composition in each of from about 12 to about 25 sites.

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